Approaches to Vaccine Development

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Spend Tax Day with the FDA

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Vaccine Development

- Complex process
- Goal is licensure of a safe, immunogenic and effective product
- The product is manufactured in a consistent way

Stages of Review and Regulation

- Phase 1 - Safety, immunogenicity (prelim)
- Phase 2 – Immunogenicity, Safety, Dose Ranging
- Phase 3 – Efficacy, Safety, Immunogenicity
- BLA – Pre-clinical and clinical data to support approval, inspection
- Phase 4 – Inspection, Safety, Efficacy, Lot Release
- BLA-Supplement (post-approval changes)

Vaccine Efficacy

- There are 3 options for showing vaccine efficacy:
  - Clinical endpoint
  - Immune response endpoints, if accepted by FDA (e.g., Hib vaccines, Hepatitis B vaccines)
  - “Animal Rule”, if certain criteria are met

Assessment of Efficacy

- Guidance for Industry – Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products (May 1998)
  - Two efficacy trials are the "standard"
  - One trial can be adequate if result is compelling, which is often the case for vaccine efficacy trials
  - Robust data, e.g., multicenter

Correlate(s) of Protection

- Interest in determining if particular type and quantity of immune response(s) is associated with protection from disease or infection caused by fully virulent pathogen(s)
- Make an assessment for an individual

Correlate(s) of Protection

- Example: HIV preventive vaccines
  - Try to identify immune correlate in efficacy trial
    - Need vaccine efficacy to find a correlate
  - Insight into what may prove to be correlate(s) in an efficacy trial might be gained from e.g.:
    - In vitro
    - Animal challenge protection trials
    - Characteristics of long-time survivors
    - Multiply exposed but uninfected persons
    - Phase 2 clinical data
    - Studies with passive products (Mab, HIVIG)

Correlate(s) of Protection

- Immune correlate(s) useful for interpreting immune response endpoints, e.g., bridging studies
- However, identification of correlate not a requirement for licensure
- Examples of vaccines licensed without an identified immune correlate of protection:
  - Acellular pertussis
  - Typhoid
  - Tuberculosis (BCG)

Vaccine Clinical Bridging Studies

- Definition of a Clinical Bridging Study:
  - Parameter(s) of interest (e.g., population, manufacturing scale, formulation, dosing schedule) is directly compared with a different version of parameter(s)
  - Purpose: To determine effect of change(s) on product's clinical performance

Vaccine Clinical Bridging Studies

- Examples of uses:
  - Address concern that manufacture changes might have resulted in a “different” vaccine no longer equivalent to previous version
  - Provide support that efficacy data can be extrapolated to a different population
    - ICH: Ethnic factors in the acceptability of foreign clinical data (1998)
  - Support new dosing schedules

Foreign clinical studies not conducted under an IND

- In general, FDA accepts such studies provided they are relevant, well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community.
- Studies meeting these criteria may be utilized to support clinical investigations in the US and/or marketing approval.

Foreign Efficacy Trials to Support US Licensure

- Vaccination against typhoid fever, Japanese encephalitis, pertussis, and hepatitis A licensed in US using foreign efficacy data
- Also need bridging studies for safety and immunogenicity, at minimum, for US licensure

Animal Rule

- Evidence needed to demonstrate effectiveness of new drugs when human efficacy studies are not ethical or practical.
- Applies to new drugs or biologics that are intended to treat or prevent life-threatening or serious conditions.

  New Drug and Biological Products; Evidence Needed to Demonstrate Efficacy of New Drugs When Efficacy Studies are Not Ethical or Feasible. 21 CFR 601.90-95, 21 CFR 314.600-650. Final rule published FR 67:37988-98; May 31, 2002.

Animal Rule

- FDA will rely on animal efficacy data when:
  - There is reasonably well understood pathophysiological mechanism for the toxicity of the substance and its prevention or substantial reduction by the product.
  - The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well characterized animal model for predicting the response in humans.

Animal Rule

- The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity.
- The data or info on the kinetics and pharmacodynamics of the product or other relevant data or info in animals and humans allow for the selection of an effective dose in humans.

Animal Rule

- The rule will apply when adequate and well-controlled clinical studies in humans cannot be ethically conducted because the studies would involve administration of a potentially lethal or permanently disabling toxic substance or organism to healthy human volunteers and field trials are not feasible prior to approval.

Animal Rule

- FDA may approve a product for which :
  - Human safety has been established.
  - Animal Rule requirements are met.

This rule does not apply if product approval can be based on standards described elsewhere in FDA's regulations.

Animal Rule

- All studies subject to the Animal Rule must be conducted in accordance with pre-existing requirements under the GLP (21 CFR 58) and the Animal Welfare Act (7 U.S.C. 2131)
- GLP will be required for the definitive/pivotal animal studies (not necessary for pilot studies). If it is in the label, the study must be conducted according to GLP.

Animal Rule

- Animal Rule Study Design Considerations:
  - Label indication (pre-exposure, post-exposure)
  - Route of exposure (mimic human exposure route)
  - Endpoints of animal studies
  - Appropriate challenge dose
  - Statistical consideration

Animal Rule

- Assay performance data: validation of both animal and human assays before pivotal/definitive studies.
- Approval Subject to Three requirements:
  - Post-marketing studies
  - Postmarketing restriction
  - Labeling for Recipients

Animal Studies: Three Requirements

- Postmarketing studies to verify and describe the product's clinical benefit when feasible and ethical. May not be feasible until an emergency arises.
- Postmarketing restrictions as needed to assure safe use, commensurate with product specific safety concerns. For example, distribution restricted to certain facilities with special experience.

Animal Studies: Three Requirements (cont.)

- Labeling for recipients
  - Provided prior to use
  - Explain that product's approval based on efficacy studies conducted in animals alone
  - Indications(s)
  - Directions for use (dosage and administration)
  - Contraindications
  - Adverse Events
  - Other relevant information

Animal Rule

- Reasons to Withdraw Approval:
  - Post-marketing clinical study fails to verify clinical benefit
  - Applicant fails to perform post-marketing study with due diligence
  - Experience shows that post-marketing restrictions are inadequate to promote safe use.
  - Applicant fails to adhere to post-marketing restrictions
  - Promotional material is false or misleading
  - Other evidence that the product is not safe or effective

Animal Rule

- Potential for Animal Rule Applications:
  - Smallpox, Anthrax, Botulism, Plague, Tularemia, Ebola
  - Each product will be reviewed on a case-by-case basis

Animal Rule

- In cases where the animal rule is planned, we recommend extensive discussion with the Agency to address important issues:
  - Development of appropriate animal models
  - Bridging from human data to animal studies

Animal Rule

- For anthrax and smallpox vaccines, there has been close collaboration between the NIH/NIAID and CBER in developing animal models for testing efficacy (e.g., weekly telecons with NIH working groups)
- Official feedback from CBER must still come through the IND and MF mechanism

Need for Expedited Pathways

- Emerging and re-emerging diseases (e.g., SARS)
- Pandemic strains of influenza
- Vaccine shortages (Prevnar, Influenza)
- New vaccines of local and global import (e.g., TB, malaria, HIV, HPV, rotavirus)
- Bioterrorism agents (Smallpox, anthrax, plague)

Mechanisms for Product Development

- Fast Track
- Priority Review
- Accelerated Approval

Fast Track

- The fast track programs are designed to facilitate the development and expedite the review of new drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs.
- Set forth in Section 112(b) of the Food and Drug Modernization Act of 1997, Section 506.
- This designation applies to the combination of the product-specific indication for which it is being studied.
- Guidance for Industry: Fast Track Development Programs-Designation, Development and Application Review – 11/18/98 (http:www.fda.gov/cber/guidelines.htm)

Fast Track

- Fast track adds to existing programs, such as accelerated approval, the possibility of a rolling submission for a marketing application.
- An important feature of fast track is that it emphasizes the critical nature of close early communication between the FDA and Sponsor to improve the efficiency of product development.
  - Fast track allows for an end-of-phase 1 meeting and other meetings (e.g., end- of -phase 2, pre-BLA) are strongly recommended.
- Fast track is intended to facilitate and get an approved product to market expeditiously

Priority Review

- A fast track product would ordinarily meet either criteria for a priority review.
- Products regulated by CBER are eligible for priority review if they provide a significant improvement compared to marketed products in the treatment, diagnosis or prevention of a serious life-threatening disease.
- Priority review – 6 month review of entire BLA from the time the last section is submitted (instead of 10 months)
- (7-valent pneumococcal conjugate vaccine)

Accelerated Approval

- FDA may grant accelerated approval based on determination that the effect of the surrogate endpoint is reasonably likely to predict clinical benefit (21 CFR 314.510 and 610.41).

Accelerated Approval

- Surrogate endpoint –was defined as a "laboratory or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, and survives and that is expected to predict the effect of therapy."(57 FR 13234 - 13235, 4/15/92)
- Codified in Modernization Act of 1997
- 2001 VRBPAC discussed preventive HPV vaccine surrogate endpoints

Emergency Use Authorization

- EUA is provided for in the Project Bioshield Act of 2004.
- The Secretary of DHHS may authorize the introduction into interstate commerce, during the effective period of declaration…of a drug, device, or biological product intended for use in an actual or potential emergency." (Emergency declared by Secretary of Defense or Homeland Security.)
- Unapproved product (benefits outweigh risks) or unapproved use of an approved product
- Only Example: Anthrax vaccine for inhalational anthrax (FR Vol. 70, #21, 2/2/05, 5450-5456).

Conclusion

- Vaccine development for emerging and re-emerging diseases is a complex issue
- There are many mechanisms already in place to help deal with the development of preventive vaccines for emerging and re-emerging diseases
- Close communication between the Sponsor and the Agency will hopefully aid in more efficient product development

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